**SUPPRESSION OF MUTANT HUNTINGTIN IMPROVES COGNITIVE SYMPTOMS IN THE R6/1 MOUSE MODEL OF HUNTINGTON’S DISEASE**

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Huntington’s disease (HD) is a monogenic neurodegenerative disorder caused by a mutation in the huntingtin (*HTT*) gene. Although HD is typically considered a motor disorder, cognitive symptoms often appear first and are the primary cause of functional decline. Our aim is to explore the effect of HTT-lowering on the cognitive state in transgenic mouse models of HD. Here, we show that R6/1 mice are impaired on spatial and recognition memory tests, indicating that the hippocampal region is affected by neurodegeneration and that HTT-lowering may ameliorate these impairments. We treated transgenic mice with ASO to suppress mutant HTT expression, and compared their cognitive performance to vehicle treated transgenic and wild-type controls. On a test of allocentric spatial memory, vehicle-treated HD mice did not learn to use the optimal spatial search strategy to escape the Barnes maze. Conversely, both wild-type and ASO-treated animals learned to use this strategy, indicating improved hippocampal function. HTT suppression also restored memory on novel object tests where ASO-treated transgenics spent significantly more time exploring novel contexts while vehicle-treated controls did not. Taken together, our data suggests that suppression of mutant HTT in early-symptomatic R6/1 mice partially improves cognitive impairments. To further enhance the cognitive state in HD mice we will consider earlier and more frequent treatment with ASO as well as combination therapy. We conclude that ASO mediated gene suppression is a promising approach for treating HD, but that additional experiments are required to reveal the optimal approach for therapeutic efficacy.

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